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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,778	04/02/2004	Gordana Vunjak-Novakovic	103248-010501	8172

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
07/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,778	VUNJAK-NOVAKOVIC ET AL.	
	Examiner	Art Unit	
	SATYENDRA K. SINGH	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-68* is/are pending in the application.

4a) Of the above claim(s) *12-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/13/2009 has been entered.

Claims 12-68, as currently amended, are pending in this application.

Claims 1-11 (applicant's elected invention; group Ia) have been previously canceled by applicants.

Claims 12-43 (directed to non-elected inventions) remain withdrawn.

Claims 44-68 (as amended; taken as applicant's elected invention of group Ia; directed to **a cartilage repair implant**; elected specie of additive "**growth factor**") are examined on their merits in this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 44-68 (as currently presented) are rejected under 35 U.S.C. 103(a) as being unpatentable over Hart et al (US 5,782,835; [A]) in view of Stone (US 6,267,786 B1; IDS), Peretti et al (2000; IDS) and Hoffman (2002; IDS).

Claims (interpreted herein as a product-by-process) are directed to "In a cartilage repair implant which includes an allograft bone plug having a subchondral bone base and an overlying cartilage cap, the improvement wherein said plug is decellularized, said decellularized plug including a sidewall that is sized and shaped such that a first portion of said sidewall engages a bore drilled in a cartilage defect area of host tissue and such that a second portion of said sidewall does not engage the bore, thereby forming a space between the bore and said second sidewall portion, the improvement further comprising an allograft milled cartilage mixture, which includes a biocompatible carrier, at least partially filling the space between the bore and said second sidewall portion of said decellularized plug to thereby enhance tissue integration between said decellularized plug and adjacent host tissue." (see instant claims 45-68 for detailed recitations)

*"[E]ven though **product-by-process claims** are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir.1985).*

Hart et al [A] (while disclosing apparatus and methods for articular cartilage repair) teach a **cartilage repair implant** (in the form of a pre-shaped bone plug; see Hart et al, abstract, summary of the invention, lines 9-14, and column 3, 4th paragraph, in particular) comprising a sterile, cylindrical shaped structure made of subchondral bone and overlying integral hyaline cartilage cap, wherein said shaped structure has been dimensioned to fit in a drilled bore in a

cartilage defect (in the form of a bone plug having a functional fit within the drilled bone hole; see Hart et al, columns 7-9, column 8, lines 50-55; and figures 8-9, in particular). Additionally, Hart et al explicitly suggest the use of various bio-adhesives (known in the art to fill the gap between the plug and the hole in the native tissue structure), and additives with the bone plug, such as bone or cartilage **growth-promoting factors** (see Hart et al, column 9, 2nd paragraph, lines 18-24, in particular), including cartilage-derived growth factor, various interleukins, platelet-derived growth factor (PDGF), and bone morphogenic protein (BMP).

However, a bone plug that has been "**decellularized**' such that bone base and cartilage cap are treated to remove cellular material (see claims 45-47), is not disclosed by the invention of Hart et al.

Stone (IDS) while disclosing non-immunogenic, proteoglycan-reduced soft tissue xenografts teaches a process wherein the immunogenicity of tissue grafts can be reduced by chemical treatment of said grafts such as washing the skeletal tissue in saline and alcohol; subjecting the graft to cellular disruption treatments; and digesting the graft with a proteoglycan depleting factor and/or glycosidase, and optionally following with a capping (i.e. chemical modifications of carbohydrate molecules on the surface of graft tissue) treatment in order to make the graft suitable for implantation purposes (see abstract, summary of the invention, and claims 20 and 21, in particular), wherein the soft tissue xenografts comprise a portion of subchondral bone, and wherein the graft can be implanted in to host cartilage defect site using biological adhesives such as fibrin clot or glue (i.e. biocompatible, polymeric carrier; see column 16, lines 45-55, in particular).

Thus, given the detailed disclosure for the benefits of decellularization of tissue grafts as taught by Stone, it would have been obvious to a person of ordinary skill in the tissue

engineering art, at the time this invention was made, to use the process disclosed by Stone in order to successfully obtain a cartilage repair implant that has been decellularized in order to remove cellular and other immunogenic materials such as proteoglycans for the benefits and suitability of implantation into host tissue without serious risk of immune rejections.

However, a cartilage repair implant comprising an **allograft milled cartilage** mixture, which includes a **biocompatible carrier** at least partially filling the space between the bore and the sidewall portion of decellularized plug, is not explicitly disclosed by the referenced inventions of Hart et al when taken with Stone.

Peretti et al (IDS) disclose the use of cell-based tissue-engineered **allogeneic** implant material for articular cartilage repair in experimental animals, wherein the implant material comprises small pieces (lamb **articular cartilage pieces** chopped under sterile conditions, lyophilized, and sorted through two different meshes to obtain specimens between the range of **500 to 1000 microns**; see Peretti et al, abstract, page 567; Materials & Methods, page 568-572; and figure 1-2, in particular) of sterile, **minced allograft cartilage mixed in thrombin/fibrinogen solution** (i.e. a biocompatible polymeric carrier) with or without allogenic chondrocyte cell preparation (see pages 568-569, in particular) in a buffered solution (such as buffered PBS) containing appropriate antibiotics. Peretti et al conclude and explicitly suggest that a composite of fibrin glue and sterile, milled allograft cartilage pieces can effectively serve as a scaffold for chondrocyte transplantation, preserve the original phenotype of the chondrocytes, and maintain the original mass of the implant, which may represent a valid option for addressing the problem of articular cartilage repair (see Peretti et al, abstract on page 567, and discussion on pages 574-575, in particular). The claimed limitations of milled cartilage being hyaline and/or fibrocartilage are also met by the disclosure of Peretti et al, wherein the

sterile, lamb cartilage chips or small pieces are used to obtain a cell-based allogenic implant construct, as discussed above.

Therefore, it would have been obvious to a person of ordinary skill in the tissue engineering art, at the time this invention was made, to modify the decellularized cartilage repair implant of Hart et al (in view of the disclosure of Stone, as discussed above) such that the decellularized bone plug is surrounded at least partially using a mixture of milled allograft cartilage pieces or mixture in a biocompatible polymeric carrier (such as a solution containing thrombin and fibrinogen), as explicitly disclosed by the invention Peretti et al.

An artisan of ordinary skill in the art would have been motivated to modify the decellularized cartilage repair implant of Hart et al (when taken with the disclosure of Stone as discussed above) because the cited prior art references suggest the incorporation of chondrogenic factors (i.e. various growth factors; Hart et al above), such that it incorporates allograft milled cartilage pieces along with chondrocytes in a biocompatible carrier (Peretti et al, see discussion above) in order to effectively address the problems associated with the articular cartilage repair (i.e. by effectively serving as an efficient scaffold for chondrocyte transplantation, preserving the original phenotype of the chondrocytes, and maintaining the original mass of the implant; see discussion, supra) with reasonable expectation of success.

However, a cartilage repair implant comprising allograft milled cartilage mixture which includes **a biocompatible carrier** such as sodium hyaluronate, gelatin, collagen, chitosan, alginate, or dextran (see recitations of instant claims 51-55 and 57, in particular), although clearly suggested (see disclosure of Hart et al, column 9, 2nd paragraph, in particular; or use of polymeric carriers such as fibrin glue, buffered PBS, etc. by Peretti et al), is not explicitly taught by the cited references of Hart et al in view of Stone and Peretti et al.

Hoffman (IDS) discloses the use of various types of polymeric materials and hydrogels such as hyaluronic acid, chitosan, gelatin, collagen, dextran, alginate, etc. in biomedical

applications, especially for use as cell and drug carriers, and as tissue engineering matrices (see Hoffman, abstract, page 3, and table 1, in particular), wherein said polymeric materials have been shown to be useful in the field of tissue engineering as matrices and/or as bioadhesive carriers, for repairing and regenerating a wide variety of tissue and organs (see page 4, left column, 1st paragraph, right column, last paragraph, and page 9, figure 5, in particular).

Thus, to an artisan of ordinary skill in the tissue engineering art, at the time this invention was made, it would have been obvious to successfully substitute biocompatible polymeric carriers that have already been well known in the art, as evidenced by the detailed disclosure of Hoffman. An artisan of ordinary skill would have been motivated to substitute biocompatible carriers to fill the space or gap between the decellularized plug (as disclosed by Hart et al in view of Stone and Peretti et al) and the sidewall, using allograft milled cartilage pieces because Hoffman clearly provides various benefits of such carriers in tissue engineering (such as for applications as porous, regenerating matrices, or for delivery of growth factors, drugs, or for various structural advantages that effectively support growth of cells responsible for tissue regeneration, etc.).

The limitations of "a cartilage repair implant which includes an allograft bone plug having a subchondral bone base and an overlapping cartilage cap" (see claim 44, in particular) is met by the combined teachings of the cited prior art references as the cartilage repair implant disclosed by Hart et al (in view of Stone, Peretti et al and Hoffman) meets all the limitations and the claimed improvement (as currently claimed), which when used in an individual of same specie (such as another human patient) would constitute as an "allograft bone plug" which has

been disclosed in the cited prior art because such limitations do no structurally change the product as currently claimed.

In addition, given the detailed teachings in the cited prior art references as discussed above, the limitations of claim 59-64 (i.e. various shapes of the allograft bone plug and diameter ranges) would have been obvious to a person of ordinary skill in the clinical art as evidenced by the fact that Hart et al disclose cylindrical grafts (see Hart et al, figure 8, column8, 2nd and 3rd paragraphs, in particular), the diameter ranges of which would have been obvious design choice depending on the type and measurement of the cartilage defects being treated. Similarly, the limitations "wherein the decellularized plug is lyophilized" to have a particular water content (see instant claims 48-49) would have been obvious to a person of ordinary skill in the tissue engineering art as evidenced by the disclosure Peretti et al that demonstrate the use of lyophilization for the preparation of milled articular cartilage specimens (see Peretti et al above). In the absence of any evidence to contrary, the shape, size, and diameter ranges of the cartilage repair implants, and the step of lyophilization to obtain the bone plug with certain water content, would have been obvious parameters for an artisan of ordinary skill in the tissue engineering art to vary and optimize depending on the parameters of the cartilage defects being treated and the stability of the decellularized bone plugs desired.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the clinical art at the time the claimed invention was made.

As per MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Obviousness-type Double Patenting

The provisional ODP rejection of record over copending application 10/438,883 (common inventors), wherein the conflicting product claims 1-42 have now been canceled by applicants (see 10/438,883; claim amendment dated 02/12/2009, and allowed method claims by the examiner's amendment on 06/04/09) is withdrawn.

Response to Applicant's Arguments

Applicant's arguments filed on 05/13/2009 with respect to claims 44-68 (as they pertain to the previous prior art rejection of record) have been considered but are not found to be persuasive for the following reasons of record:

Regarding the 103(a) rejection of record, applicants argue the following (see remarks, pages 13-15, in particular):

> "With respect to amended independent Claim 44, it recites a cartilage repair implant which includes an **allograft plug** (i.e., a graft of bone tissue from another individual of the same species as the recipient). In contrast to the allograft bone plug recited in independent Claim 44, the Hart Patent discloses an **autograft** bone plug (118) that is harvested from the patient him~ or herself, and is subsequently implanted back into the patient's body. According to the specification of the Hart et al. Patent, during surgery, the autograft bone plug (118) is removed from a non-weight-bearing surface of the patient's joint (see col. 8, lines 36-49) and is then inserted into a bone hole (120) drilled into the bone at the site of a defect (110) in the patient's articular cartilage (112) (see col 9, lines 26-54). The Hart et al. Patent neither discloses nor suggests that the bone plug (118) may be an allograft, and therefore differs from the allograft plug of independent Claim 44.
>
> Independent Claim 44 also recites that the allograft bone plug is **decellularized**. As conceded by the Examiner in the Office Action, the Hart et al. Patent does not disclose that the autograft bone plug (118) is decellularized. Any such decellularization treatment andfor processing of the autograft bone plug (118) would delay the immediate implantation of the autograft bone plug (118), and would have to be performed **separately** from the surgical procedure disclosed in the Hart et al. Patent, thereby complicating and delaying that surgical procedure and being contrary to tile intended purpose of the Hart et al. Patent. Treating the autograft bone plug (t18) as postulated by the Examiner would therefore defeat the purpose of the single surgical procedure disclosed in the Hart et al. Patent, and compromise any benefits obtained by performing such single surgical procedure. The Hart et al. Patent therefore **teaches away** from any modifications whereby the autograft bone plug (118) would be treated using the processes disclosed in the Stone Patent (i.e., subjecting the plug to a cellular disruption treatment and digesting the plug with a proteoglycan-depleting factor, and/or performing other processing steps thereon). For similar reasons, applicants' attorney respectfully submits that the Hart et al. Patent **teaches away** from performing any other treatment and/or processing steps (e.g., the processing steps of dependent Claims 45-47) on the autograft bone plug (118). For the foregoing reasons, applicants' attorney respectfully submits that one skilled in the tissue engineering art would **not** subject the fresh autograft Hart et al. Patent plug to the time-consuming processing steps disclosed in the Stone Patent."

In response, it is noted that instant claims are directed to "a cartilage repair implant" (i.e. a product) as specifically recited in claim 44 as currently amended, which has been disclosed and/or made obvious by the cartilage repair implant disclosed by the prior art reference of Hart et al (in view of Stone, Peretti et al, and Hoffman; see the rejection above), albeit exemplified as being used for the repair of the cartilage defect in the donor itself (thus being argued by applicants as being an "autograft"). As discussed above in the obviousness rejection of record, the designations of "autograft" and "allograft" signifies the donor-recipient relationship (i.e. autograft, when used in the same subject or patient that is when donor and recipient are the same, and allograft, when used in a different subject/patient of same species that is when the donor and recipient are not the same) and does not impart any structural feature(s) in the "cartilage repair implant" claimed as an improvement by applicants. The implant disclosed in view of the cited prior art references of record teaches all the features recited in the claim, and would have been obvious to an artisan of ordinary skill in the art at the time this invention was made. Therefore, applicant's arguments are noted and fully considered, but they are not found to be persuasive for these reasons.

The argument that the reference of Hart et al teaches away from the claimed invention is not found to be persuasive because instant claims are directed to a product-by-process, and since, the same product (albeit used differently) is disclosed and/or made obvious by the cited prior art references, the obviousness rejection of record over the claimed product is proper. The argument that "*Hart et al Patent teaches away from performing any other treatment and/or processing steps*.." is fully considered, but is not found to be persuasive because the structural features of the product recited in the instant claim are fully met and/or made obvious by the

combined teachings of the cited prior art references. Thus, the 103(a) rejection of record is properly made.

Conclusion

NO claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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